Supplementary Online Content

Rebbeck TR, Mitra N, Wan F, et al. Association of type and location of *BRCA1* and *BRCA2* mutations with risk of breast and ovarian cancer. *JAMA*.

doi:10.1001/jama.2014.5985

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Mutation Nomenclature

Mutations are described using the Human Genome Variation Society (HGVS) nomenclature (http://www.hgvs.org/mutnomen) in which the nucleotide numbering is from the A of the ATG translation initiator codon. For deletions or insertions the most 3' position possible is arbitrarily assigned to have been changed. The description of mutations is given at the genomic level (using cDNA reference sequences NM_007294.3 / *BRCA1* and NM_000059 / *BRCA2*). BIC nomenclature also is presented for common variants that are familiar to many researchers and clinicians by their BIC designation (http://research.nhgri.nih.gov/bic). For BIC nomenclature, cDNA sequences are used as reference sequence (Genbank: U14680 / *BRCA1* and NM_000059.1/ *BRCA2*). The nucleotide numbering begins at nucleotide 1 of the cDNA sequence. For deletions or insertions the most 3' position possible was arbitrarily assigned to represent the mutation position in this nomenclature.

eAppendix 2. Penetrance Estimation

Let RR be the relative risk/hazard estimated from our data, and p(Y=0|X) be the survivor function. Then

$$P(Y=0 \mid X=1) = \exp[-\Lambda_0(\tau) \, RR]$$

$$P(Y=0 \mid X=0) = \exp[-\Lambda_0(\tau)]$$

Where $\Lambda_0(\tau)$ is the hazard function. Therefore,

$$P(Y=0 \mid X=1) = P(Y=0 \mid X=0)^{RR} \tag{1}$$

In order to estimate the penetrance P(Y=1|X=0),

$$P(Y=1) = P(Y=1|X=1) \, P(X=1) + P(Y=1|X=0)(PX=0) \tag{2}$$

Substituting Equation (1) into Equation (2), we have

$$P(Y=1) = (1-P(Y=0|X=0)^{RR}) \, P(X=1) + (1-P(Y=0|X=0)^{RR}) \, P(X=0) \tag{3}$$

P(Y=1) is available from the BOADICEA model[1], and the values of P(X=1) and P(X=0) are available from the CIMBA data set. In this example, we use mutation prevalence estimates from the UK EMBRACE study sample as the reference population (http://www.cancerresearchuk.org/about-cancer/trials/a-study-of-people-who-have-faulty-breast-cancer-genes). We solve Equation (3) numerically for P(Y=0|X=0). Then P(Y=1|X=1) can be computed as $1 - P(Y=0|X=0)^{RR}$.

To compute 95% confidence intervals (95%CI), we assume the value of the variance of RR is known, and β is the estimate of P(Y=0 | X=0). The variance of these two estimators is σ^2_{RR} and σ^2_{β}, respectively. To compute the variance of $1-P(Y=0 \mid X=0)^{RR}$, we apply the multivariate delta method such that

$$
\begin{aligned}
g(RR, \beta) &= P(Y=1 \mid X=1) \\
&= 1 - P(Y=0 \mid X=0)^{RR} \\
&= 1 - \beta^{RR}.
\end{aligned}
$$

Then

$$\frac{dg(RR, \beta)}{d(RR)} = -RR\,\beta^{RR-1}$$

$$\frac{dg(RR, \beta)}{d(\beta)} = -\beta^{RR}\ln(RR)$$

Assuming the two estimators have no correlation, the variance of $1 - \beta^{RR}$ is

$$\mathrm{var}\,(1 - \beta^{RR}) = [-RR\,\beta^{RR-1} \quad -\beta^{RR}\ln(RR)]\begin{bmatrix}\sigma^2_{RR} & 0 \\ 0 & \sigma^2_{\beta}\end{bmatrix} \times \begin{bmatrix} -RR\,\beta^{RR-1} \\ -\beta^{RR}\ln(RR)\end{bmatrix}$$

$$= (RR\,\beta^{RR-1})^2\,\sigma^2_{RR} + (\beta^{RR}\ln(RR))^2\,\sigma^2_{\beta}$$

We compute RR, β, σ^2_{RR}, σ^2_{β} using the data available to us as described in the main text.

This provides us with $1 - \beta^{RR}$, which can be used to compute a 95% CI as

$$1 - \beta^{RR} + 1.96\sqrt{\mathrm{var}\,(1 - \beta^{RR})}$$

Reference

1.   Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. *Br J Cancer.* 2008;98(8):1457-1466.

eAppendix 3. Funding Acknowledgements

The DKFZ study was supported by the DKFZ, Heidelberg, Germany, the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan and the Pontificia Universidad Javeriana, Bogota, Colombia.

EMBRACE

EMBRACE is supported by Cancer Research UK Grants C1287/A10118 and C1287/A11990. D. Gareth Evans and Fiona Lalloo are supported by an NIHR grant to the Biomedical Research Centre, Manchester. The Investigators at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust are supported by an NIHR grant to the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. Ros Eeles and Elizabeth Bancroft are supported by Cancer Research UK Grant C5047/A8385.

FCCC

The authors acknowledge support from the Fox Chase Cancer Center and The University of Kansas Cancer Center and the Kansas Bioscience Authority Eminent Scholar Program. A.K.G. was funded by 5U01CA113916, R01CA140323, P30 CA168524 and by the Chancellors Distinguished Chair in Biomedical Sciences Professorship. M.B.D. and E.A.R. were funded by
P50 CA083638, P30 CA06920 and 3U01 CA69631.

GC-HBOC

The German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) is kindly supported by the German Cancer Aid to R. K. Schmutzler (grant no 109076).*GEMO*
The study was supported by the Ligue National Contre le Cancer; the Association "Le cancer du sein, parlons-en!" Award; and the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program.

Georgetown

The study was supported by the Fisher Center for Familial Cancer Research, the Familial Cancer Registry at Georgetown University (NIH/NCI grant P30-CA051008), and Swing Fore the Cure.

GOG

This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group (GOG) Administrative Office and Tissue Bank (CA 27469), the GOG Statistical and Data Center (CA 37517), and GOG's Cancer Prevention and Control Committee (CA 101165).

HCSC

This research was supported by Spanish Ministry of Economy and Competitivity, grants PI12/oo539 and RD12/0036/0006 (ISCIII).

HEBCS

The HEBCS was financially supported by the Helsinki University Central Hospital Research Fund, the Sigrid Juselius Foundation, the Finnish Cancer Society, and the Academy of Finland (132473).

HEBON

The HEBON study is supported by the Dutch Cancer Society grants NKI1998-1854, NKI2004-3088, NKI2007-3756, the Netherlands Organization of Scientific Research grant NWO 91109024, the Pink Ribbon grant 110005 and the BBMRI grant NWO 184.021.007/CP46.

HRBCP

HRBCP is supported by The Hong Kong Hereditary Breast Cancer Family Registry and the Dr. Ellen Li Charitable Foundation, Hong Kong.

HUNBOCS

Hungarian Breast and Ovarian Cancer Study was supported by Hungarian Research Grant KTIA-OTKA CK-80745 and the Norwegian EEA Financial Mechanism HU0115/NA/2008-3/ÖP-9.

ICO

Contract grant sponsor: Asociación Española Contra el Cáncer, Spanish Health Research Fund; Carlos III Health Institute; Catalan Health Institute and Autonomous Government of Catalonia. Contract grant numbers: ISCIIIRETIC RD06/0020/1051, PI10/01422, PI10/00748 and 2009SGR290.

eAppendix 4. Acknowledgements

BCFR
We wish to thank members and participants in the New York site of the Breast Cancer Family Registry for their contributions to the study.
BMBSA
We wish to thank the families who contribute to the BMBSA study.
BRICOH
We wish to thank Yuan Chun Ding, Greg Wilhoite, and Marie Pinto for their work in participant enrollment and biospecimen and data management.
CNIO
We thank Alicia Barroso, Rosario Alonso and Guillermo Pita for their assistance.
CONSIT TEAM
We would like to thank Monica Barile of the Istituto Europeo di Oncologia, Milan, Italy; Liliana Varesco of the IRCCS AOU San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.
DKFZ
We are grateful to all the patients for their participation. We thank the physicians and other hospital staff, scientists, research assistants and study stuff who contributed to the patient recruitment, data collection, sample preparation and molecular analyses.
EMBRACE
Epidemiological study of *BRCA1* & *BRCA2* mutation carriers (EMBRACE): EMBRACE Collaborating Centres are: Coordinating Centre, Cambridge: Debra Frost, Steve Ellis, Radka Platte. North of Scotland Regional Genetics Service, Aberdeen: Zosia Miedzybrodzka, Helen Gregory. Northern Ireland Regional Genetics Service, Belfast: Patrick Morrison. West Midlands Regional Clinical Genetics Service, Birmingham: Trevor Cole, Jonathan Hoffman. South West Regional Genetics Service, Bristol: Alan Donaldson, Margaret James. East Anglian Regional Genetics Service, Cambridge: Amy Taylor. Medical Genetics Services for Wales, Cardiff: Alexandra Murray, Mark T. Rogers. St James's Hospital, Dublin & National Centre for Medical Genetics, Dublin: M. John Kennedy. South East of Scotland Regional Genetics Service, Edinburgh: Peninsula Clinical Genetics Service, Exeter: Carole Brewer. West of Scotland Regional Genetics Service, Glasgow: Rosemarie Davidson, Victoria Murday, Nicola Bradshaw, Lesley Snadden, Mark Longmuir, Catherine Watt, Sarah Gibson, Ed Tobias, Alexis Duncan. South East Thames Regional Genetics Service, Guy's Hospital London: Louise Izatt, Chris Jacobs. Leicestershire Clinical Genetics Service, Leicester: Julian Barwell. Yorkshire Regional Genetics Service, Leeds: Julian Adlard. Cheshire & Merseyside Clinical Genetics Service, Liverpool: Ian Ellis. Manchester Regional Genetics Service, Manchester: D Gareth Evans, Fiona Lalloo, Jane Taylor. North East Thames Regional Genetics Service, NE Thames, London: Lucy Side, Alison Male. Nottingham Centre for Medical Genetics, Nottingham: Jacqueline Eason. Northern Clinical Genetics Service, Newcastle: Oonagh Claber, Irene Jobson. Oxford Regional Genetics Service, Oxford: Dorothy Halliday, Sarah Durell. The Institute of Cancer Research and Royal Marsden NHS Foundation Trust: Ros Eeles, Susan Shanley, Nazneen Rahman, Elizabeth Bancroft, Elizabeth Page, Audrey Ardern-Jones, Kelly Kohut, Jennifer Wiggins, Elena Castro, Anita Mitra. North Trent Clinical Genetics Service, Sheffield: Jackie Cook, Oliver Quarrell, Cathryn Bardsley. South West Thames Regional Genetics Service, London: Shirley Hodgson, Glen Brice, Vishakha Tripathi, Virginia Attard. Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton: Diana Eccles, Anneke Lucassen, Gillian Crawford, Donna McBride.
FCCC
We thank Ms. JoEllen Weaver and Dr. Betsy Bove for their technical support.
GC-HBOC
We are very thankful to all family members who participated in this study.
GEMO
Genetic Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers (GEMO) study : National Cancer Genetics Network «UNICANCER Genetic Group», France. We wish to thank all the

GEMO collaborating groups for their contribution to this study. GEMO Collaborating Centers are: Coordinating Centres, Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Hospices Civils de Lyon - Centre Léon Bérard, & Equipe «Génétique du cancer du sein», Centre de Recherche en Cancérologie de Lyon: Olga Sinilnikova†, Sylvie Mazoyer, Francesca Damiola, Laure Barjhoux, Carole Verny-Pierre, Mélanie Léone, Nadia Boutry-Kryza, Alain Calender, Sophie Giraud; and Service de Génétique Oncologique, Institut Curie, Paris: Dominique Stoppa-Lyonnet, Marion Gauthier-Villars, Bruno Buecher, Claude Houdayer, Etienne Rouleau, Lisa Golmard, Agnès Collet, Virginie Moncoutier, Cédrick Lefol, Muriel Belotti, Antoine de Pauw, Camille Elan, Catherine Nogues, Emmanuelle Fourme, Anne-Marie Birot. Institut Gustave Roussy, Villejuif: Brigitte Bressac-de-Paillerets, Olivier Caron, Marine Guillaud-Bataille. Centre Jean Perrin, Clermont–Ferrand: Yves-Jean Bignon, Nancy Uhrhammer. Centre Léon Bérard, Lyon: Christine Lasset, Valérie Bonadona, Sandrine Handallou. Centre François Baclesse, Caen: Agnès Hardouin, Pascaline Berthet, Dominique Vaur, Laurent Castera. Institut Paoli Calmettes, Marseille: Hagay Sobol, Violaine Bourdon, Tetsuro Noguchi, Audrey Remenieras, François Eisinger. CHU Arnaud-de-Villeneuve, Montpellier: Isabelle Coupier, Pascal Pujol. Centre Oscar Lambret, Lille: Jean-Philippe Peyrat, Joëlle Fournier, Françoise Révillion, Philippe Vennin†, Claude Adenis. Centre Paul Strauss, Strasbourg: Danièle Muller, Jean-Pierre Fricker. Institut Bergonié, Bordeaux: Emmanuelle Barouk-Simonet, Françoise Bonnet, Virginie Bubien, Nicolas Sevenet, Michel Longy. Institut Claudius Regaud, Toulouse: Christine Toulas, Rosine Guimbaud, Laurence Gladieff, Viviane Feillel. CHU Grenoble: Dominique Leroux, Hélène Dreyfus, Christine Rebischung, Magalie Peysselon. CHU Dijon: Fanny Coron, Laurence Faivre. CHU St-Etienne: Fabienne Prieur, Marine Lebrun, Caroline Kientz. Hôtel Dieu Centre Hospitalier, Chambéry: Sandra Fert Ferrer. Centre Antoine Lacassagne, Nice: Marc Frénay. CHU Limoges: Laurence Vénat-Bouvet. CHU Nantes: Capucine Delnatte. CHU Bretonneau, Tours: Isabelle Mortemousque. Groupe Hospitalier Pitié-Salpétrière, Paris: Florence Coulet, Chrystelle Colas, Florent Soubrier, Mathilde Warcoin. CHU Vandoeuvre-les-Nancy : Johanna Sokolowska, Myriam Bronner. CHU Besançon: Marie-Agnès Collonge-Rame, Alexandre Damette. Creighton University, Omaha, USA: Henry T. Lynch, Carrie L. Snyder.
G-FAST
We wish to thank the technical support of Ilse Coene and Brecht Crombez.
HEBCS
HEBCS would like to thank Drs. Carl Blomqvist and Kirsimari Aaltonen for their help with the HEBCS data and samples.
HEBON
The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON) consists of the following Collaborating Centers: Coordinating center: Netherlands Cancer Institute, Amsterdam, NL: M.A. Rookus, F.B.L. Hogervorst, S. Verhoef, M.K. Schmidt, J.L. de Lange; Erasmus Medical Center, Rotterdam, NL: J.M. Collée, M.J. Hooning, C.H.M. van Deurzen, I.M. Obdeijn; Leiden University Medical Center, NL: C.J. van Asperen, J.T. Wijnen, R.A.E.M. Tollenaar, P. Devilee, T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center, NL: C.M. Kets, A.R. Mensenkamp; University Medical Center Utrecht, NL: M.G.E.M. Ausems, R.B. van der Luijt; Amsterdam Medical Center, NL: C.M. Aalfs, T.A.M. van Os; VU University Medical Center, Amsterdam, NL: J.J.P. Gille; University Hospital Maastricht, NL: E.B. Gómez-Garcia, M.J. Blok; University Medical Center Groningen, NL: J.C. Oosterwijk, A.H. van der Hout, M.J. Mourits. The Netherlands Foundation for the detection of hereditary tumours, Leiden, NL: H.F. Vasen.
HRBCP
We wish to thank Hong Kong Sanatoriuma and Hospital for their continual support.
HUNBOCS
We wish to thank to Hungarian Breast and Ovarian Cancer Study Group members and the clinicians and patients for their contributions to this study.
ICO
We wish to thank the ICO Hereditary Cancer Program.
INHERIT

We would like to thank Dr Martine Dumont, Martine Tranchant for sample management and skillful technical assistance.

IPOBCS
We would like to thank Dr. Patrícia Rocha and Dr. Catarina Santos for their contribution for *BRCA1/BRCA2* genetic testing in IPOBCS.

KCONFAB
We wish to thank Heather Thorne, Eveline Niedermayr, all the kConFab research nurses and staff, the heads and staff of the Family Cancer Clinics, and the many families who contribute to kConFab.

MOD SQUAD
The Czech Republic investigators were supported by MH CZ-DRO (MMCI, 00209805), the European Regional Development Fund, and the State Buget of the Czech Republic (RECAMO, CZ1.05/2.1.00/03.0101.

OSU CCG
Kevin Sweet and Michelle O'Connor were instrumental in accrual of study participants, ascertainment of medical records and database management. Samples were processed by the OSU Human Genetics Sample Bank.

SEABASS
We would like to thank the doctors, research nurses, and research assistants involved in the MyBrCa Study, Singapore Breast Cancer Study and the HUKM-HKL Study (Malaysia) for assistance in patient recruitment, data collection and sample preparation.

SWE-BRCA
Swedish scientists participating as SWE-BRCA collaborators are part of the Swedish national cancer genetics network representing Lund University and University Hospital, Gothenburg Sahlgrenska University Hospital, Stockholm and Karolinska University Hospital, Umeå University Hospital, Uppsala University and Linköping University Hospital.

UCHICAGO
We wish to thank Cecilia Zvocec, Qun Niu, physicians, genetic counselors, research nurses and staff of the Cancer Risk Clinic for their contributions to this resource, and the many families who contribute to our program.

UCLA
We thank Lorna Kwan, MPH for assembling the data for this study.

UCSF
We would like to thank Dr. Robert Nussbaum and the following genetic counselors for participant recruitment: Beth Crawford, Kate Loranger, Julie Mak, Nicola Stewart, Robin Lee, Amie Blanco. And thanks to Ms. Salina Chan for her data management.

UKFOCR
We acknowledge the Roswell Park Alliance Foundation for their continued support of the Gilda Radner Ovarian Family Cancer Registry.

UPENN
We would like acknowledge our genetic counselor Jill Stopfer for participant recruitment, our laboratory and database managers, Kurt D'Andrea, and Jessica Tigges-Cardwell for their contributions to this work, as well as the rest of the staff of the McDonald Cancer Risk Evaluation Program and the Basser Center for BRCA.

VFCTG
We thank Marion Harris and Martin Delatycki of the Victorian Familial Cancer Trials Group. We thank Sarah Sawyer and Rebecca Driessen for assembling this data.

eTable 1. Study Sample - Numbers of Individuals with *BRCA1* or *BRCA2* Mutations by Center and Cancer Status

Center ID	Study Name	Country	*BRCA1* Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total *BRCA1*	*BRCA2* Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total *BRCA2*	TOTAL
BCFR	Breast Cancer Family Registry	USA/Canada/Australia	383	35	29	221	668	295	13	9	213	530	1,198
BFBOCC	Baltic Familial Breast Ovarian Cancer Consortium	Latvia/Lithuania	87	91	18	52	248	7	2	0	1	10	258
BIDMC	Beth Israel Deaconess Medical Center	USA	32	4	0	1	37	22	3	0	28	53	90
BMBSA	BRCA-gene mutations and breast cancer in South African women	South Africa	43	8	8	17	76	98	12	3	43	156	232
BRICOH	Beckman Research Institute of the City of Hope	USA	80	28	7	140	255	53	9	4	90	156	411
CBCS	Rigshospitalet	Denmark	121	62	19	33	235	82	14	3	19	118	353
CNIO	Spanish National Cancer Centre	Spain	122	28	28	100	278	189	20	7	143	359	637
COH	City of Hope Cancer Center	USA	125	17	12	81	235	121	5	2	54	182	417
CONSIT TEAM	CONsorzio Studi ITaliani sui Tumori Ereditari Alla Mammella	Italy	372	165	86	258	881	348	33	28	160	569	1,450
DEMO-KRITOS	National Center for Scientific Research "Demokritos"	Greece	115	39	14	26	194	14	0	0	3	17	211
DFCI	Dana Farber Cancer Institute	USA	66	11	8	78	163	54	4	2	79	139	302
DKFZ	German Cancer Research Center	Germany Pakistan/Colombia	148	15	7	85	255	41	5	2	35	83	338
DNA HEBON	Genen Omgeving studie van de	Netherlands	553	99	47	621	1,320	280	40	20	501	841	2,161

			BRCA1					BRCA2					
Center ID	Study Name	Country	Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA1	Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA2	TOTAL
EMBRACE	werkgroep Hereditiair Borstkanker Onderzoek Nederland Epidemiological Study of Familial Breast Cancer	UK	529	90	64	539	1,222	445	55	21	520	1,041	2,263
FCCC	Fox Chase Cancer Center	USA	50	16	6	51	123	45	13	4	50	112	235
GC-HBOC	German Familial Breast Group	Germany	1,030	200	108	468	1,806	579	47	26	312	964	2,770
GEMO	Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers	France/ USA	895	223	141	559	1,818	684	56	23	274	1,037	2,855
GEORGE-TOWN	Georgetown University	USA	27	3	2	19	51	17	3	0	21	41	92
GOG	Gynecologic Oncology Group	USA	227	0	0	240	467	161	0	0	160	321	788
HCSC	Hospital Clinico San Carlos	Spain	66	21	12	78	177	77	9	3	74	163	340
HEBCS	Helsinki Breast Cancer Study	Finland	47	10	11	28	96	64	6	7	51	128	224
HRBCP	Study of Genetic Mutations in Breast and Ovarian Cancer patients in Hong Kong and Asia	Hong Kong	21	5	5	13	44	41	0	1	19	61	105
HUNBOCS	Molecular Genetic Studies of Breast- and Ovarian Cancer in Hungary	Hungary	105	23	6	54	188	36	5	0	21	62	250
HVH	University Hospital Vall d'Hebron	Spain	34	6	4	26	70	39	3	1	25	68	138
ICO	Institut Català d'Oncologia	Spain	81	27	11	72	191	118	16	9	91	234	425
IHCC	International Hereditary Cancer	Poland	638	143	28	673	1,482	14	8	1	12	35	1,517

Center ID	Study Name	Country	BRCA1					BRCA2					TOTAL
			Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA1	Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA2	
ILUH	Centre Iceland Landspitali - University Hospital	Iceland	5	0	3	0	8	145	2	10	33	190	198
INHERIT	INterdisciplinary HEalth Research Internal Team BReast CAncer susceptibility	Canada (Quebec)	48	13	4	53	118	51	5	3	58	117	235
IOVHBOCS	Istituto Oncologico Veneto	Italy	70	50	17	28	165	98	14	8	31	151	316
IPOBCS	Portuguese Oncology Institute-Porto Breast Cancer Study	Portugal	28	14	5	50	97	66	2	2	53	123	220
KCONFAB	Kathleen Cuningham Consortium for Research into Familial Breast Cancer	Australia/ New Zealand	363	44	29	290	726	301	21	9	253	584	1,310
KOHBRA	Korean Hereditary Breast Cancer Study	Korea	99	1	6	26	132	153	1	2	62	218	350
MAGIC	Modifiers and Genetics in Cancer	USA	35	11	2	66	114	32	4	1	52	89	203
MAYO	Mayo Clinic	USA	159	33	16	160	368	100	14	5	88	207	575
MCGILL	McGill University	Canada (Quebec)	25	2	2	30	59	17	1	0	25	43	102
MDAND	MD Anderson Cancer Center	USA	103	22	5	54	184	0	0	0	0	0	184
MOD-SQUAD	Modifier Study of Quantitative Effects on Disease	Czech Republic/ Belgium	185	43	23	45	296	93	10	5	35	143	439
MSKCC	Memorial Sloane Kettering Cancer Center	USA	201	29	15	117	362	148	23	2	86	259	621
MUV	General Hospital Vienna	Austria	214	37	28	185	464	126	6	7	86	225	689

Center ID	Study Name	Country	BRCA1					BRCA2					TOTAL
			Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total *BRCA1*	Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total *BRCA2*	
NCI	National Cancer Institute	USA	40	10	4	98	152	18	5	1	51	75	227
NNPIO	N.N. Petrov Institute of Oncology	Russia	89	20	6	14	129	3	0	0	0	3	132
OCGN	Ontario Cancer Genetics Network	Canada	73	33	14	115	235	69	21	1	90	181	416
OSU CCG	The Ohio State University Comprehensive Cancer Center	USA	66	8	7	47	128	55	11	2	37	105	233
OUH	Odense University Hospital	Denmark	147	60	18	201	426	134	16	7	164	321	747
PBCS	Università di Pisa	Italy	47	16	12	23	98	42	2	0	14	58	156
SEABASS	South East Asian Breast Cancer Association Study	Malaysia/ Singa- pore	41	7	3	6	57	32	0	1	4	37	94
SMC	Sheba Medical Centre	Israel	301	133	21	340	795	167	42	7	179	395	1,190
SWE-BRCA	Swedish Breast Cancer Study	Sweden	215	97	43	212	567	85	20	2	68	175	742
UCHICAGO	University of Chicago	USA	36	3	6	44	89	39	6	1	22	68	157
UCLA	University of California Los Angeles	USA	42	6	3	59	110	26	3	0	45	74	184
UCSF	University of California San Francisco	USA	44	24	3	49	120	46	7	3	38	94	214
UKGRFOCR	UK and Gilda Radner Familial Ovarian Cancer Registries	UK/USA	25	103	11	45	184	4	21	2	12	39	223
UPENN	University of Pennsylvania	USA	229	47	30	148	454	147	16	9	123	295	749
VFCTG	Victorian Familial Cancer Trials Group	Australia	71	20	11	6	108	42	12	2	13	69	177
WCP	Women's Cancer Program at	USA	54	62	13	127	256	17	16	4	45	82	338

Center ID	Study Name	Country	BRCA1					BRCA2					TOTAL
			Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total *BRCA1*	Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total *BRCA2*	
	Cedars-Sinai Medical Center												
TOTAL			**9,052**	**2,317**	**1,041**	**7,171**	**19,581**	**6,180**	**682**	**272**	**4,766**	**11,900**	**31,481**

eTable 2. Bins and Risks Used to Define Ovarian and Breast Cancer Cluster Regions (Depicted in Figure 2): *BRCA1*

Bin	Putative Region*	Bin Starting Nucleotide	Bin Ending Nucleotide	N	N (Breast Cancer)	HR, 95% CI (Breast Cancer)	N (Ovarian Cancer)	HR, 95%CI (Ovarian Cancer)	Ratio (HR-Breast: HR-Ovarian) (95%CI)	P-Value
1		1	67	151	84	1.17 (0.93,1.48)	23	0.90 (0.60,1.33)	1.31 (0.82-2.09)	0.265
2		68	69	2328	1036	0.89 (0.82,0.96)	392	0.94 (0.83,1.07)	0.94 (0.81-1.10)	0.456
3		70	178	243	146	1.24 (1.04,1.48)	54	0.97 (0.73,1.27)	1.28 (0.94-1.75)	0.116
4	BCCR1	179	181	984	546	1.11 (1.01,1.22)	118	0.74 (0.61,0.89)	**1.50 (1.21-1.85)**	**<0.001**
5	BCCR1	182	505	403	239	1.17 (1.03,1.34)	62	0.87 (0.67,1.12)	**1.35 (1.00-1.82)**	**0.048**
6		506	927	407	218	0.98 (0.85,1.13)	75	0.94 (0.75,1.18)	1.05 (0.80-1.38)	0.750
7		928	1116	398	198	0.89 (0.77,1.02)	81	0.96 (0.77,1.20)	0.92 (0.70-1.22)	0.573
8		1117	1379	370	167	1.00 (0.86,1.17)	55	1.07 (0.82,1.40)	0.94 (0.68-1.29)	0.686
9	OCCR	1380	1674	377	165	0.81 (0.69,0.95)	82	1.31 (1.05,1.63)	**0.62 (0.47-0.82)**	**0.001**
10		1675	1892	399	208	0.91 (0.80,1.05)	90	1.10 (0.89,1.36)	0.83 (0.64-1.08)	0.172
11	OCCR	1893	2071	390	168	0.84 (0.72,0.99)	76	1.20 (0.94,1.54)	**0.70 (0.52-0.94)**	**0.019**
12	OCCR	2072	2338	396	180	0.78 (0.67,0.91)	70	1.04 (0.81,1.33)	**0.75 (0.56-0.99)**	**0.049**
13	OCCR	2339	2475	450	210	0.88 (0.77,1.00)	94	1.21 (1.00,1.48)	**0.72 (0.56-0.93)**	**0.010**
14		2476	2685	448	208	0.89 (0.77,1.03)	73	1.05 (0.83,1.33)	0.85 (0.64-1.13)	0.251
15	OCCR	2686	3013	399	175	0.84 (0.73,0.98)	91	1.30 (1.05,1.61)	**0.65 (0.50-0.85)**	**0.001**
16	OCCR	3014	3254	378	164	0.79 (0.68,0.92)	96	1.23 (1.00,1.52)	**0.64 (0.48-0.85)**	**0.002**
17		3255	3331	393	180	0.90 (0.77,1.05)	78	1.12 (0.89,1.41)	0.80 (0.61-1.07)	0.131
18		3332	3482	373	179	0.86 (0.75,1.00)	84	1.13 (0.90,1.42)	0.76 (0.58-1.01)	0.059
19		3483	3661	398	196	0.85 (0.74,0.98)	62	0.84 (0.64,1.10)	1.02 (0.74-1.40)	0.910
20		3662	3753	384	187	0.93 (0.80,1.07)	68	1.13 (0.91,1.41)	0.82 (0.63-1.08)	0.152
21		3754	3770	406	210	1.00 (0.87,1.15)	88	1.14 (0.93,1.41)	0.88 (0.67-1.14)	0.326
22		3771	4016	350	148	0.93 (0.79,1.11)	67	0.95 (0.73,1.25)	0.98 (0.70-1.36)	0.892
23	OCCR	4017	4062	321	118	0.65 (0.53,0.78)	101	1.11 (0.87,1.41)	**0.58 (0.42-0.81)**	**0.001**
24		4063	4167	419	217	1.20 (1.04,1.38)	67	1.15 (0.92,1.43)	1.04 (0.79-1.37)	0.761
25		4168	4327	513	281	1.18 (1.04,1.34)	82	0.99 (0.79,1.24)	1.20 (0.92-1.56)	0.186
26	BCCR2	4328	4945	417	252	1.16 (1.02,1.32)	67	0.86 (0.68,1.11)	**1.34 (1.01-1.78)**	**0.042**
27		4946	5123	486	270	1.00 (0.88,1.13)	90	0.93 (0.75,1.16)	1.07 (0.83-1.39)	0.605
28		5124	5260	361	224	1.17 (1.02,1.34)	67	0.90 (0.70,1.16)	1.30 (0.97-1.74)	0.076
29	BCCR2	5261	5266	3052	1666	1.20 (1.13,1.27)	459	0.92 (0.83,1.02)	**1.30 (1.14-1.48)**	**<0.001**
30	BCCR2	5267	5563	482	289	1.30 (1.15,1.47)	65	0.79 (0.62,1.01)	**1.65 (1.25-2.17)**	**<0.001**

*BCCR: breast cancer cluster region, OCCR: ovarian cancer cluster region

eTable 3. Bins and Risks Used to Define Ovarian and Breast Cancer Cluster Regions (Depicted in Figure 3): *BRCA2*

Bin	Putative Region*	Bin Starting Nucleotide	Bin Ending Nucleotide	N	N (Breast Cancer)	HR, 95%CI (Breast Cancer)	N (Ovarian Cancer)	HR, 95% CI (Ovarian Cancer)	Ratio (HR-Breast: HR-Ovarian)	P-Value
1	BCCR1	1	596	663	391	1.17 (1.04,1.32)	33	0.68 (0.43,1.08)	**1.72 (1.06-2.78)**	**0.028**
2		597	771	586	381	1.11 (0.96,1.29)	43	1.13 (0.76,1.68)	0.98 (0.64-1.51)	0.931
3	BCCR1'	772	1806	623	364	1.08 (0.97,1.20)	31	0.66 (0.46,0.96)	**1.63 (1.11-2.40)**	**0.014**
4		1807	2786	573	310	0.96 (0.85,1.08)	39	0.83 (0.60,1.14)	1.16 (0.82-1.66)	0.399
5		2787	3248	611	332	0.98 (0.88,1.10)	42	0.88 (0.64,1.21)	1.12 (0.79-1.59)	0.524
6	OCCR1	3249	3847	590	285	0.78 (0.69,0.88)	61	1.38 (1.07,1.78)	**0.57 (0.42-0.76)**	**0.000**
7	OCCR1	3848	4478	535	264	0.91 (0.80,1.03)	57	1.38 (1.05,1.80)	**0.66 (0.49-0.89)**	**0.007**
8	OCCR1	4479	5238	555	251	0.80 (0.70,0.90)	57	1.19 (0.89,1.59)	**0.67 (0.48-0.93)**	**0.017**
9	OCCR1	5239	5681	523	280	0.98 (0.87,1.10)	56	1.54 (1.15,2.04)	**0.64 (0.47-0.87)**	**0.005**
10		5682	5945	611	357	1.09 (0.98,1.22)	43	0.87 (0.63,1.20)	1.26 (0.89-1.77)	0.188
11	OCCR1	5946	5946	1341	579	0.74 (0.64,0.86)	155	1.27 (0.99,1.63)	**0.58 (0.45-0.76)**	**0.000**
12		5947	6275	612	322	1.07 (0.96,1.20)	41	0.80 (0.58,1.09)	1.35 (0.96-1.90)	0.090
13		6276	6644	542	301	0.95 (0.85,1.07)	43	0.99 (0.73,1.34)	0.97 (0.69-1.35)	0.841
14	OCCR2	6645	7471	582	302	0.85 (0.74,0.97)	64	1.49 (1.12,1.97)	**0.57 (0.41-0.80)**	**0.001**
15		7472	7933	571	320	1.09 (0.96,1.23)	47	1.03 (0.73,1.45)	1.06 (0.74-1.52)	0.759
16	BCCR2	7934	8535	752	455	1.19 (1.07,1.33)	43	0.50 (0.34,0.74)	**2.37 (1.56-3.59)**	**0.000**
17	BCCR2	8536	8904	507	302	1.27 (1.11,1.44)	31	0.60 (0.39,0.92)	**2.12 (1.34-3.35)**	**0.001**
18		8905	9118	565	345	1.22 (1.08,1.39)	34	0.93 (0.60,1.46)	1.31 (0.82-2.11)	0.264
19		9119	9925	558	311	1.07 (0.96,1.20)	34	0.73 (0.52,1.04)	1.46 (0.99-2.14)	0.054